CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21548/S28 & 22116/S12
Priority or Standard	Priority
Submit Date(s)	10/28/11
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Division / Office	DAVP/OAP
Reviewer Name(s)	Neil Rellosa, MD
Review Completion Date	4/4/12
Established Name	Fosamprenavir calcium
(Proposed) Trade Name	Lexiva®
Therapeutic Class	HIV-1 protease inhibitor
Applicant	Viiv Healthcare Company
Formulation(s)	700 mg tablet & 50 mg/mL oral suspension
Dosing Regimen	Calculated based on age and body weight
Indication(s)	Treatment of HIV infection with ritonavir
Intended Population(s)	Pediatric patients aged 4 weeks to less than 6 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The NDA for Lexiva® (fosamprenavir) Oral Solution and Tables indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks to less than 6 years of age should be approved. Based on review of the submitted pharmacokinetic (PK) data and further analyses performed by the Clinical Pharmacology reviewers, adjustments to the Applicant's proposed dosing were made for labeling. The final dosing recommendations based on adjustments by weight and previous protease inhibitor status are summarized in Table 1 below:

Table 1: Twice-Daily Dosage Regimens for PI-Naïve Pediatric Patients ≥4 Weeks of Age and for PI-Experienced ≥6 Months of Age Using FPV Oral Suspension With Concurrent RTV

Patient's weight	Recommended Dosage Regimen
<11 kg	FPV/RTV 45/7 mg/kg BID[a]
11- <15 kg	FPV/RTV 30/3 mg/kg BID[a]
15- <20 kg	FPV/RTV 23/3 mg/kg BID[a]
≥20 kg	FPV/RTV 18/3 mg/kg BID[a]

[a] When dosing with RTV, do not exceed the adult dose of FPV 700 mg/RTV 100 mg BID

For pediatrics, the data are insufficient to recommend once-daily dosing of LEXIVA alone or in combination with RTV or dosing of LEXIVA alone or in combination with RTV for PI-experienced children less than 6 months of age. Further, twice-daily dosing of LEXIVA alone in pediatric patients less than 2 years of age has not been studied, so no dosing recommendation for this age group can be made.

1.2 Risk Benefit Assessment

Although there may be limited use for Lexiva in the younger age groups of HIV-I infected children, the need for more antiretroviral medication options is warranted especially in resource limited areas. The submitted data indicate that Lexiva, an already FDA approved product, can be safe and effective for use across a wide spectrum of pediatric patients with no increased risk of serious adverse events or development of viral resistance as compared to adult patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Post-marketing surveillance is already in place for older pediatric populations and adults and similar surveillance should performed in younger patients covered in this submission. Surveillance of neutropenia should be considered based on the data submitted here. The Lexiva labeling contains patient labeling. No further risk mitigation strategies are necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for additional postmarket requirements or commitments. A waiver was previously granted in 2007 for pediatric patients less than 1 month of age and all other pediatric age groups have been studied. As such, the Applicant will be released from previous postmarket requirements for pediatric data.

2 Introduction and Regulatory Background

With the advancement in the treatment of HIV over the last decade, pediatric HIV patients are living longer and over time these patients may develop complex associated medical issues and viral resistance patterns that call for the need for broader treatment options. As outlined by the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children of The Health Resources and Services Administration of The National Institutes of Health (NIH) in the August 11, 2001 *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, treatment regimens that contain protease inhibitors remain effective treatment and relatively safe to use. Currently, there are nine protease inhibitors approved for use; seven of which have pediatric formulations and are approved for use in children at varying age increments.

Fosamprenavir calcium (FPV, Leviva®), a phosphate ester pro-drug of the HIV-1 protease inhibitor (PI) amprenavir (APV) was initially developed to reduce pill burden and pill size/volume size for use in the treatment of HIV-1 infection in adults. The drug was initially approved for use, both with and without concurrent ritonavir (RTV), in combination therapy for the treatment of HIV-1 infected adults on October 20, 2003. At the time of initial approval, the Applicant entered into an agreement under a Written Request to collect data to determine the safety, effectiveness and dosing in the pediatric population.

An initial NDA for a 50 mg/mL oral suspension for use in pediatric patients 2-5 years of age without RTV, and with RTV in patients 6 years of age and older was initially approved on June 14, 2007. Under the initial approval in 2007, a wavier was granted for completion of trials for patients aged birth to one month of age. The waiver was based on the fact that FPV is unlikely to be used in children less than one month of age

because probable need to dose it with RTV which has not been demonstrated to be safe and effective for use in patients in this age group.

This supplemental NDA extends the dosing indication of FPV co-administration with RTV (FPV/RTV) to include patients 4 weeks to less than 6 years of age and broaden the effective treatment options made available to a larger number of pediatric patients.

2.1 Product Information

Leviva®, an antiretroviral agent, is a phosphate ester pro-drug of APV that has similar attributes of APV while demonstrating improved water solubility. APV, a small peptidomimetic protease inhibitor, acts on HIV-1 and HIV-2 protease late in the HIV replication process after the virus enters the cell's nucleus by binding to the protease activity site and prevents the enzyme from cleaving viral polyprotein precursors into functional proteins and overall preventing the formation of infectious viral particles. FPV is a potent CYP3A4 isoenzyme inhibitor. RTV is also an anti-HIV PI, but is often used to inhibit host enzymes that metabolize other PIs, such as FPV. This inhibition leads to higher plasma concentrations of these latter drugs, allowing for lower doses and frequency of administration. Currently, FPV is approved for the use in combination therapy with RTV for pediatric patients 6 years of age and older and without RTV for pediatric patients 2-5 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

Overall, there are three main classes of antiretroviral agents used for the treatment of HIV-1 infection in pediatric patients: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and PIs. Currently, there are seven PIs including FPV approved for use in children at varying age increments. Table 2 provides a listing of these PIs:

Table 2: Protease Inhibitors Approved for Use in Pediatric Patients for the Treatment of HIV-1 Infection

Protease Inhibitor	Age Group Approved for Use	Formulation
Reyataz® (atazanavir)	6 to 18 years of age boosted with RTV	capsules
Prezista® (darunavir)	6 to 18 years of age boosted with RTV	tablets
Lexiva® (fosamprenavir)	2 to 5 years of age unboosted with RTV; 6 to 18 years of age boosted with RTV	tablets and oral suspension

Kaletra® (lopinavir/ritonavir)	14 days to 18 years of age	tablets and oral suspension
Viracept® (nelfinavir)	2 to 18 years of age	tablets and powder for oral suspension
Norvir® (ritonavir)	>1 month of age to boost other PIs	capsules and oral solution
Aptivus® (tipranavir)	2 to 18 years of age boosted with RTV	capsules and oral solution

2.3 Availability of Proposed Active Ingredient in the United States

LEXIVA Oral Solution and Tablets are commercially available in the United States and approved for use in adult patients and the previous mentioned pediatric age groups. Lexiva Oral Solution is available as 50 mg/mL and Tablets as 700 mg. APV or Agenerase® in its previous various formulations was withdrawn from the US market in 2009 at the Applicant's request.

2.4 Important Safety Issues With Consideration to Related Drugs

Protease inhibitors are metabolized hepatically; therefore, there is potential for multiple drug interactions. FPV is a potent CYP3A4 isoenzyme inhibitor and some drugs are contraindicated for concominant use. In addition, PIs may be associated with metabolic complications such as dyslipidemia, fat maldistribution and insulin resistance.

Gastrointestinal intolerance is one of the major adverse events associated with PIs. Some previous studies have shown increased adverse events with gastrointestinal tolerance, specifically vomiting, with FPV in children as compared to adults, however in older children the safety profile of FPV is similar to that seen in adult patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On December 26, 2001 an initial Written Request (WR) for pediatric studies was issued calling for multiple-dose pharmacokinetic and safety studies to be performed in combination with low-dose RTV in patients from birth to 17 years of age.
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In June 10, 2002, the WR was amended to study patients from 4 weeks to 17 years of age. Multiple other amendments were made that included the addition of resistance as a clinical endpoint (2002), changes in dosage (2002 and 2003), and changes in the timeframe for submitting reports (2002, 2006 and 2009).

FPV as 700 mg tablets, both with and without concurrent ritonavir, was initially approved on October 20, 2003 for the treatment of adults with HIV-1 infection. The oral suspension was approved for use in combination therapy without boosting with RTV for

pediatric patients 2 years of age and older on June 14, 2007. (b) (4)

The study designs for the studies for this submission were previously reviewed and agreed upon based on the amended Written Request. At that time, it was determined that the proposed type of trial design could properly evaluate the safety, tolerability, pharmacokinetics and antiviral activity of FPV for patients 4 weeks to less than 6 years of age.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

To ensure that the submitted data is of good quality and integrity, in conjunction with Clinical Pharmacology, a DSI consult was submitted on December 6, 2011 for BE/GLP inspections which would included verification of clinical data (HIV-1 RNA levels and CD4+ counts at baseline, Week 12, Week 24, and Week 48) at three study sites (two from APV20002 in South Africa and Mexico, one from APV29005 in South Africa).

Results from these inspections found that the data for this submission from the audited sites was acceptable. However, from APV29005, one sample from a subject on Day 336 of the study was analyzed outside the duration of demonstrated stability. The Division of Bioequivalence and GLP Compliance (DBGC) questioned the accuracy of data for this sample and recommended not accepting the data from this sample in the review.

Medical Officer's (MO's) Comment: It is unlikely this one sample significantly affected the pharmacokinetic, efficacy or safety results of this study. The quality and integrity of the data for this submission is appropriate for review.

3.2 Compliance with Good Clinical Practices

It appears that the clinical trials were conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards.

3.3 Financial Disclosures

The Financial Disclosure forms were reviewed. Many investigators and sub-investigators had no disclosures to report in all three studies. It is unlikely that any of the

financial relationships outlined below could potentially bias or affect the outcome of a particular study.

In APV20002, eight sub-investigators were not located and therefore their complete required information regarding financial interests or arrangements was not available. Initial information available internally to the Applicant did not indicate any potential disclosable financial interests for these 8 investigators.

In APV29005, fourteen sub-investigators were not located and therefore their complete required information regarding financial interests or arrangements was not available. Initial information available internally to the Applicant did not indicate any potential disclosable financial interests for these 14 investigators. In addition, based on enrollment, none of these investigators were deemed as a potential risk that could affect the outcome of this study. One sub-investigator, Dr. (b) (6) site was listed as a part or full time employee of the Applicant. According to the Applicant, Dr. (b) (6) participated as a sub-investigator during (b) (6) fellowship at this site until (b) (6). (b) (6) then became an employee of the Applicant following (b) (6) fellowship and assumed the role of Medical Monitor for study (b) (6) but no longer acted as a sub-investigator for this study. The Applicant reports that Dr. (b) (6) had no disclosable financial interests during (b) (6) time as a sub-investigator. In addition, only (b) (6) patients were enrolled at this site.

In APV20003, eight sub-investigators and one principal investigator were not located and therefore their complete required information regarding financial interests or arrangements was not available. Initial information available internally to the Applicant did not indicate any potential disclosable financial interests for these investigators. On addition, the one principal investigator, Dr. only enrolled patients.

One other principal investigator, Dr. (b) (6) reported financial interests/arrangements. Dr. (b) (6) received a total of $133,623 in grants and honoraria from the Applicant. However, (b) (6) recruited (b) (6) subjects from a total of (b) (6) subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Lexiva Oral Solution and Tablets are approved products. No new chemistry manufacturing or control information was supplied with this supplement.

4.2 Clinical Microbiology

Please refer to the Virology review by Dr. Lalji Mishra for further details. In studies APV20002 and APV 29005, 20 of the total 163 subjects were deemed virologic failure (VF) during the first 24 weeks on treatment. However, the majority of these subjects were antiviral experienced at baseline and their prior antiviral therapies and baseline viral drug resistance may have affected their final outcomes. In addition, only 4 subjects developed treatment-emergent PI resistance-associated mutations. The mutations observed were those known to occur in patients treated with either fosamprenavir or amprenavir.

4.3 Preclinical Pharmacology/Toxicology

No further Pharmacology/Toxicology information was included in this submission. The pharmacological and toxicological profiles of both FPV and APV have previously and extensively been investigated.

4.4 Clinical Pharmacology

Mechanism of Action

FPV is a prodrug that is hydrolyzed to APV, a HIV-1 protease inhibitor, by cellular phosphatases as it is being absorbed in the gut epithelium. APV inhibits HIV-1 protease by binding to its active site and preventing the processing of viral Gag and Gag-Pol polyprotin precursors. This results in the formation of non-infectious viral particles. FPV itself has little or no antiviral activity in vitro.

4.4.2 Pharmacodynamics

No new pharmacodynamics information was included for either product in this submission.

4.4.3 Pharmacokinetics

From APV20002 and APV29005, a total of 66 subjects between 4 weeks and less than 6 years of age received FPV/RTV BID regimens and provided evaluable APV PK data. Doses ranged between 20 and 60 mg of FPV and between 3 and 10 mg of RTV, depending on age.

(b) (4) In order to better understand how to target doses in this age range clinical pharmacology modeling and simulations was conducted. These analyses suggested improved pharmacokinetics when dosing was based on a combination of age and weight and a closer match to the

pharmacokinetics observed in PI-naïve adults. Dosing for PI-experienced subjects less than 6 months of age was not recommended because these patients were not studied and there is a lack of sufficient data to formulate a dosing recommendation.

The tables below show the Applicant's and FDA's proposed dosing regimens. For the purpose of labeling, the FDA analysis will be used.

Table 3: The Applicant's Proposed Dosing Regimen By Weight of FPV with Concurrent RTV

Table 4: FDA's Proposed Twice-Daily Dosage Regimens for PI-Naïve Pediatric Patients ≥4 Weeks of Age and for PI-Experienced ≥6 Months of Age Using FPV Oral Suspension With Concurrent RTV

Patient's weight	Recommended Dosage Regimen
<11 kg	FPV/RTV 45/7 mg/kg BID[a]
11- <15 kg	FPV/RTV 30/3 mg/kg BID[a]
15- <20 kg	FPV/RTV 23/3 mg/kg BID[a]
≥20 kg	FPV/RTV 18/3 mg/kg BID[a]

[a] When dosing with RTV, do not exceed the adult dose of FPV 700 mg/RTV 100 mg BID

MO's Comment: Please see Dr. Dionna Green's and Jeff Florian's Clinical Pharmacology reviews for further discussion and details on the pharmacokinetic issues of this submission. Further dosing recommendations will be discussed in Section 6.1.8.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Two pivotal studies, APV20002 and APV29005, were submitted for review for safety and efficacy in this supplement. APV20002 was submitted to cover the pediatric age group from 4 weeks to less than 2 years of age. APV29005 was submitted to cover the pediatric age group from 2 years to less than 6 years of age. Study APV20003 was submitted as a supportive study for safety in the age group from 2 years to less than 6 years of age.

Study, Protocol No.	Study Design	No. of Centers and Locations	Study Population	Treatment Regimen, Dose, & Duration	Efficacy Analysis Population
Pivotal Study					
APV20002	Phase II, uncontrolled, non-randomized, open-label, 2-cohort, multicenter study to evaluate PK, safety, tolerability, antiviral response	7 centers; 3 in South Africa, 2 in Mexico, 1 each in Argentina & Portugal	HIV-1 infected PI-naïve & PI-experienced patients aged 4 weeks to <2 years	FPV suspension (50mg/mL); 30, 45 60 mg/kg PO BID; ≥48 weeks with or without RTV RTV solution (80mg/mL); 6, 7, 10 mg/kg PO BID; ≥48 weeks with or without RTV	Total No. of patients=54; Male 23 Female 31 Age range= 2-24 months Mean age= 6 months
APV29005	Phase II, uncontrolled, non-randomized, open-label, multi-cohort, multicenter study to evaluate PK, safety, tolerability, antiviral response	30 centers; 10 in US, 2 in Canada, 1 in Belgium, 9 in Spain, 3 in Russia, 2 in Romania, 3 in South Africa	HIV-1 infected PI-naïve & PI-experienced patients aged 2 to 18 years	FPV tablet (700 mg) PO BID; ≥48wks with RTV FPV suspension (50 mg/mL); 15, 18, 23, 30 or 40 mg/kg PO BID; ≥48wks with or without RTV RTV capsule (100 mg) PO BID; ≥48wks RTV solution (80 mg/mL); 3 mg/kg PO BID; ≥48wks	Total No. of patients=109; Male 51 Female 58 Age range= 2-18 years Mean age= 9 years
Supporting Study					
APV 20003	Phase II, uncontrolled, non-randomized, open-label, multi-cohort, multicenter study to evaluate PK, safety, tolerability, antiviral response	38 centers; 13 in US, 9 in Spain, 8 in Italy, 3 in Portugal, 2 in Canada, 2 in Romaina, 1 in Netherlands	HIV-1 infected ART-naïve & ART-experienced patients aged 2 to 18 years	FPV tablet (700 mg); 1400mg PO daily (with switch to 700 mg PO BID in 10 subjects); ≥48wks with RTV FPV suspension (50 mg/mL); 30 mg/kg PO daily or for those who switched 15, 20 mg/kg PO BID; ≥48wks with RTV RTV capsule (100 mg); 200 mg PO daily or 100 mg PO BID; ≥48wks RTV solution (80 mg/mL); 6 mg/kg PO daily or 3, 4 mg/kg PO BID; ≥48wks	Total No. of patients=69; Male 30 Female 39 Age range= 2-17 years Mean age= 10 years

5.2 Review Strategy

The clinical information provided by the Applicant from the two pivotal studies was reviewed. These studies were Phase II, uncontrolled, non-randomized and no formal statistical hypothesis testing was performed. The efficacy and safety results of these studies were mainly evaluated from a descriptive perspective. Unless there were specific issues pertaining to an individual study, the integrated data were reviewed and presented. These studies are reviewed in detail in Section 6: Review of Efficacy and Section 7: Review of Safety. Submitted material that was reviewed included the clinical study overview and summary, clinical study reports on efficacy and safety, data sets, and individual case report forms. The proposed label was also reviewed and revisions were recommended based on the provided information.

Study APV20003 evaluated once-daily dosing of FPV with RTV however the data from this study were insufficient to support once-daily dosing regimens in any pediatric population. Therefore, data from APV20003 was only evaluated and reviewed as supportive to the overall safety and PK analysis and not efficacy of this product for subjects aged 2 years to less than 6 years.

Since these are already approved products and there are no new data or information for certain disciplines such as pharmacology/toxicology, full reviews for these disciplines were not included. Because of these studies were conducted as pharmacokinetics studies, many of the clinical review conclusions and recommended label changes are based on analysis and input from Clinical Pharmacology. The review for Clinical Pharmacology is summarized in Section 4.4 however for a more detailed analysis of the clinical pharmacology issues for this submission refer to the full review by Dr. Dionna Green.

5.3 Discussion of Individual Studies/Clinical Trials

APV20002 Study Design

APV20002 was a Phase II, open-label, 2-cohort, multicenter study and was conducted in subjects aged 4 weeks to less than 2 years with HIV-1 infection and looked to evaluate the PK, safety, tolerability, and antiviral activity of FPV at different dosing regimens. Subjects were enrolled into one of two cohorts: Cohort 1A contained subjects 6 months to less than 2 years and Cohort 2A contained subjects 4 weeks to less than 6 months of age.

Subjects in Cohort 1A initially had a single dose visit (SDV) where they received a single 30 mg/kg dose of FPV followed by a second SDV where they received a single 30/6 mg/kg dose of FPV/RTV.

Subjects in Cohort 2A initially also received a single 30 mg/kg dose of FPV at their first SDV but then received a single 45/7 mg/kg dose of FPV/RTV at their second SDV.

Subjects then received dosing with a FPV/RTV BID regimen based on the single dose PK results. Additional subjects were enrolled but did not undergo SDVs and were initiated on FPV/RTV BID regimens based on PK results from previously enrolled subjects.

Study center visits for evaluation were made at Weeks 2, 4, 8, 12, 16, 24, 36 and 48 weeks. Serial blood samples were obtained for determination of plasma APV, FPV, and RTV concentrations and pharmacokinetic evaluation over 12 hours at the first SDV and at Weeks 2 or 8. In addition, two samples were collected at the second SDV and one sample was obtained at all other visits.

Evaluations for safety and tolerability included both clinical and laboratory parameters. Clinical assessments included: height, weight, vital signs, concomitant medications, and adverse events (AEs). Laboratory evaluations included: hematology, clinical chemistry, serum lipase, non-fasting lipids, and serum α-1 acid glycoprotein.

Evaluations for antiviral and immunologic response included: quantitative plasma HIV-1 RNA, lymphocyte total and subsets, HIV associated conditions, and HIV-1 resistance testing.

Health outcome evaluations were also performed and included a parent/guardian perception of study medication questionnaire.

APV20002 Inclusion/Exclusion Criteria

Major inclusion criteria were the following:

- Male or female 4 weeks to less than 2 years of age
- Screening plasma HIV-1 RNA level greater than or equal to 400 copies/mL
- Subjects, who in the investigator's opinion, and following viral resistance testing if conducted, were able to construct an active nucleoside reverse transcriptase inhibitor (NRTI) backbone regimen consisting of 2 NRTIs
- Therapy-naïve or PI-naïve defined as having received less than one week of any PI
- PI-experienced defined as having prior experience with no more than three PIs

Major exclusion criteria were the following:

- Prior history of receiving Agenerase (AGN)
- Non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the study
- PI therapy within 5 days prior to study drug administration for those subjects undergoing SDVs

- Subjects in the acute phase of a CDC Clinical Category C event or infection at Baseline
- Presence of a malabsorption syndrome or other gastrointestinal dysfunction which might interfere with drug absorption or ability to orally take study drug
- Presence of a serious medical condition that might compromise the safety of the subject
- Any acute laboratory abnormality at screen that should preclude participation including Grade 3 or higher serum aminotransferase levels
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents, immunodmodulating agents, or any agent with known anti-HIV activity within 28 days of study drug administration

APV29005 Study Design

APV29005 was a Phase II, open-label, multi-cohort, multicenter study and was conducted in PI-naïve and PI-experienced subjects aged 2 to 18 years with HIV-1 infection and looked to evaluate the PK, safety, tolerability, and antiviral activity of FPV at different dosing regimens. Subjects were enrolled into one of 5 cohorts as shown in the Table 5 below:

Table 5: APV29005 Study Design

Cohort	Age[a]	Treatment Status	Regimen[b]
1A[c]	2 to <6	PI-naïve	FPV BID
1B[c]	2 to <6	PI-naïve or experienced	FPV/RTV BID
2[c]	6 to 12	PI-naïve or experienced	FPV/RTV BID
3[c]	12 to 18	PI-naïve or experienced	FPV/RTV BID (pill regimen)
4[d]	2 to 18	PI-naïve or experienced	FPV/RTV BID

a. Subjects may enrol up to one month before 6th birthday (Cohorts 1A and 1B), one month before 12th birthday (Cohort 2), and one month before 19th birthday (Cohorts 3 and 4). Enrolment = Baseline/Day 1.
b. GlaxoSmithKline will provide optional ABC and/or 3TC to all subjects for use in constructing a backbone regimen.
c. Cohorts 1A, 1B, 2 and 3 will enrol in parallel. Subjects in these cohorts will have a PK profile on Week 2 and PK trough sampling on Weeks 4, 8, 12, 16, 24, 36 and 48 and every 12 weeks thereafter.
d. Subjects in Cohort 4 will have PK trough sampling on Weeks 2, 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter

Adapted from the APV29005 Study Report Body Section 4.1 Study Design

Cohort 4 enrollment started once enrollment in any given age defined cohort (Cohort 1A, 1B, 2 and 3) was complete.

Subjects in Cohort 1A (2 to <6 years) initially received a FPV BID regimen and subjects in Cohorts 1B, 2, and 3 (12 to 18 years) initially received a FPV/RTV BID regimen from Baseline. The first 6 to 10 subjects in each cohort initiated a dosage regimen based on previous APV and FPV pediatric studies. Subsequently, enrolled subjects initiated a dosage regimen based on PK data from the first 6 to 10 subjects enrolled in their

respective cohort. For all subjects, the dosage regimen may have been adjusted based on the individual's steady-state PK results collected at Week 2 or later.

FPV was administered as either 700 mg tablets or 50 mg/mL oral suspension while the RTV was administered as either 100 mg capsules or 80 mg/mL oral solution.

Study center visits for evaluation were made at Weeks 2, 4, 8, 12, 16, 24, 36 and 48 weeks. Serial blood samples from Cohorts 1A, 1B, 2 and 3 were obtained for determination of plasma APV, FPV, and RTV concentrations and pharmacokinetic evaluation over 8 or 12 hours at Week 2, with a single PK trough sample collected at subsequent visits. For Cohort 4, a single PK trough sample was obtained at Week 2 and at all following visits.

Evaluations for safety and tolerability included both clinical and laboratory parameters. Clinical assessments included: height, weight, vital signs, concomitant medications, and AEs. In additionally, assessments of fat redistribution and lipodystrophy were collected. Laboratory evaluations included: hematology, clinical chemistry, serum lipase, fasting lipids, insulin, glucose and serum α-1 acid glycoprotein.

Evaluations for antiviral and immunologic response included: quantitative plasma HIV-1 RNA, lymphocyte total and subsets, HIV associated conditions, and HIV-1 resistance testing.

Subject adherence was also assessed with questionnaires.

APV29005 Inclusion/Exclusion Criteria
Major inclusion criteria were the following:

- Male or female 2 to 18 years of age
- A female of non-childbearing potential or child-bearing potential with a negative serum pregnancy test at screen, a negative urine pregnancy test on Day 1 and who agreed to use an approved contraception method
- Screening plasma HIV-1 RNA greater than or equal to 400 copies/mL
- Subjects who are therapy-naïve or PI-naïve subjects defined as having received less than one week of any PI and any length of therapy with NRTIs and/or NNRTIs
- Subjects who are PI-experienced defined as having received greater than one week prior PI therapy with no more than three PIs

Major exclusion criteria were the following:

- Prior history of receiving AGN or FPV for greater than 7 days
- Non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the study

- Subjects in the acute phase of a CDC Clinical Category C event or infection at Baseline
- Presence of a malabsorption syndrome or other gastrointestinal dysfunction which might interfere with drug absorption or ability to orally take study drug
- Presence of a serious medical condition that might compromise the safety of the subject
- Pregnant or lactating females
- Any acute laboratory abnormality at screen that should preclude participation including Grade 3 or 4 serum aminotransferase levels within 28 days prior to study drug administration and/or clinically relevant episodes of hepatitis within the previous 6 months
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents, immunodmodulating agents, or any agent with known anti-HIV activity within 28 days of study drug administration
- Substantial non-adherence based on history

Supportive Study (APV20003) Design

APV20003 was a Phase II, open-label, multi-cohort, multicenter study and was conducted in therapy-naïve and therapy-experienced subjects aged 2 to 18 years with HIV-1 infection and looked to evaluate the PK, safety, tolerability, and antiviral activity of FPV at different dosing regimens. Subjects were enrolled into one of 5 cohorts as shown in the Table 6 below:

Table 6: APV20003 Study Design

		Number of Subjects
Cohort[1]	**Age**	**ART-naïve[2] and ART-experienced[3]** FPV/RTV once daily
1	2 to < 6 years	16
2	6 to < 12 years	12
3	12 to 18 years	10
4[4,5]	2 to 18 years	24

1. Cohorts 1, 2 and 3 enrolled in parallel. Subjects in these cohorts had PK trough sampling on Weeks 8, 12, 24 and 48 and a PK profile on Week 4.
2. ART-naïve subjects received abacavir sulfate (ABC)/ lamivudine (3TC).
3. GlaxoSmithKline provided **optional** ABC and/or 3TC to ART-experienced subjects whose HIV-1 genotype showed susceptibility to ABC and/or 3TC.
4. Subjects were permitted to enroll in Cohort 4 when enrollment of the appropriate number of similarly aged subjects in Cohorts 1, 2 or 3 was completed.
5. Subjects in Cohort 4 had PK trough sampling on Weeks 4, 8, 12, 24 and 48.

Adapted from the APV20003 Study Report Body Section 5.1 Overall Study Design

FPV was administered as either 700 mg tablets or 50 mg/mL oral suspension while the RTV was administered as either 100 mg capsules or 80 mg/mL oral solution.

MO's Comment: The details of the dosing regimens, PK evaluations, and antiviral and immunologic assessments are not included here since this study was only used as a supportive study for safety.

Evaluations for safety and tolerability included both clinical and laboratory parameters. Clinical assessments included: height, weight, vital signs, concomitant medications, hepatitis status, and adverse events (AEs). Laboratory evaluations included: hematology, clinical chemistry, serum lipase and lipids

Major inclusion and exclusion criteria for APV20003 were similar to APV29005.

6 Review of Efficacy

Efficacy Summary

Overall, in both APV20002 and APV29005 virologic success, defined as having a viral load of less than 400 copies/mL at Week 24, was seen in the majority of subjects. In addition improvement of CD4+ cell counts and percent CD4+ cell counts were in all treatment cohorts including those who received FPV alone or boosted with RTV.

In APV20002, 39 of the 54 subjects (72%) in this study achieved virologic success and only 10 subjects were deemed virological failures. This effect was even greater at Week 48 with 79% of subjects having a viral load less than 400 copies/mL, although a smaller number of subjects were still enrolled in the study at that time (n=38) In addition, significant proportions of subjects had viral loads less than 50 copies/mL at Week 24 (46%) and at Week 48 (79%).

In APV29005, overall 70 of the 109 subjects (64%) in this study achieved virologic success and 33 subjects were deemed virological failures. The smallest portion of virologic success was the PI-experienced subjects treated with RTV boosted FPV (55%). Viral loads less than 400 copies/mL were seen in 58 of 74 subjects (78%) at Week 48. Only 45% of subjects had viral loads less than 50 copies/mL at Week 24, but 68% of subjects had viral loads less than 50 copies/mL at Week 48.

In general, in both studies the subjects were relatively representative of children with HIV infection. However, there were some limitations in distributions of age, gender and race which make it difficult to make absolute conclusions about differences in efficacy, but no substantial differences were seen in subpopulation analyses.

6.1 Indication

The proposed indication is: Lexiva is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks to less than 6 years of age.

6.1.1 Methods

For both studies, APV20002 and APV29005, the following evaluations were performed to assess efficacy:

- Quantitative plasma HIV-1 RNA (Roche Ultrasensitive HIV-1 Monitor Test; version 1.5, limit of detection (LOD) = 50 copies/mL). Samples with >75,000 copies/mL were retested using the Roche HIV-1 Monitor Test, version 1.5, standard LOD=400 copies/mL

- Lymphocyte subsets including total lymphocytes, absolute and percent CD4+ and CD8+ cell counts

- HIV-associated conditions: The subject was assessed for any new or recurring HIV-associated condition at each visit (Day 1 onward)

In addition, HIV Genotypic Resistance testing (b) (4) was performed in both studies.

Because both APV20002 and APV 29005 were designed to mainly evaluate dosing and PK data, antiviral and immunologic response endpoints were secondary. These endpoints included:

- Proportion of subjects with plasma HIV-1 RNA less than 400 copies/mL and less than 50 copies/mL over time
- Changes from baseline in HIV-1 RNA over time
- Changes from baseline in CD4+ cell counts and CD4+ cell percentages over time

Due to the open-label, non-comparative design of these studies, no formal statistical hypothesis testing was performed. Descriptive methods were used to analyze the antiviral response data.

The primary analysis population for the antiviral response was the Intent-to-Treat Exposed (ITT[E]) defined as all subjects who received at least one dose of the study drug. Analyses of this population included the Missing, Switch or Discontinuation equals Failure (MSD=F) and Observed analyses.

MO's Comment: As stated previously, the methodology to evaluate the efficacy of Lexiva was previously reviewed and based on the amended Written Request issued by FDA on December 26, 2001. At that time, it was agreed that this methodology could properly evaluate the antiviral activity of FPV for patients 4 weeks to less than 6 years of age.

6.1.2 Demographics

The integrated demographic and characteristics of the integrated ITT[[E] population depicted in Table 7 below:

Table 7: Demographic and Characteristics of Integrated ITT[E] Population from Baseline

Demographic Characteristic	Study APV29005		Study APV20002
	FPV N=20	FPV/RTV N=89	FPV/RTV N=54
Age (months/years)[a]			
Median, years (Range)	2.5 (2, 5)	11 (2, 18)	
Median, months (Range)			6 (2,24)
Sex, n (%)			
Female	15 (75)	43 (48)	31 (57)
Male	5 (25)	46 (52)	23 (43)
Ethnicity, n (%)			
Hispanic or Latino	0	15 (17)	9 (17)
Non-Hispanic or Latino	20 (100)	74 (83)	45 (83)
Race, n (%)			
White / Caucasian	19 (95)	41 (46)	2 (4)
Black	0	43 (48)	44 (81)
Arabic / North African	0	1 (1)	0
South Asian	0	1 (1)	0
Other	1 (5)	3 (3)	8 (15)

Data Source: Study APV29005, Table 6.14 and Table 6.18; Study APV20002, Table 6.9 and Table 6.10
a. For APV29005 age is shown in years, for APV20002 age is shown in months

In both studies, sex was overall well matched; however, in APV29005 there was a female predominance in the group of patients who received only FPV.

The majority of the subjects in both studies were either White/Caucasian or Black. However in APV20002 an overwhelming majority of subjects (88%) were Black with a small or no representation of other races including White/Caucasian. In APV29005, almost all subjects in the FPV only group were White/Caucasian.

On closer review of the age distribution of subjects in APV20002 (see Table 8 below), there were no patients younger than 2 months of age in the 4 weeks to less than 6 months age group.

Table 8: Baseline Age Distributions of ITT[E] Population of APV20002

	4 weeks to <6 months N=26	6 months to <2 years N=28	Total N=54
Age (months), median (range)	3 (2, 5)	13 (6, 24)	6 (2, 24)

Adapted from APV20002 Study Report in Section 5.4 Demographic and Baseline Characteristics

MO's Comment: This submission is seeking to broaden the current pediatric dosing range to include patients less than 2 months of age; however, no patients under 2 months of age were enrolled. As discussed above in Section 4.4.3, the Applicant performed simulated PK modeling and calculated plasma APV exposures for patients 1 to less than 24 months of age. These simulated exposures were consistent with effective exposures seen in previous adult studies. Based on this exposure data and antiviral responses in other pediatric age groups with FPV and with similar PIs, it is reasonable to speculate that FPV would have similar antiviral and immunologic response in subjects between 4 weeks and 2 months of age.

There were unequal distributions of race and gender in certain aspects of both studies; however, this was likely due to the overall small number of subjects enrolled in each trial.

In terms of baseline clinical characteristics, the majority of the subjects in both studies were either classified by CDC Classification in Children less than 13 as Class N (non-symptomatic) or Class A (mildly symptomatic). The subjects who were adolescents were mostly classified by CDC Classification as Class A (asymptomatic) or Class B (symptomatic, not AIDS). Vertical/perinatal transmission was the most common known HIV risk factor in both studies and for APV29005, the majority of subjects had non-reactive testing for Hepatitis B and C. These results are summarized in Table 9 below:

Table 9: Baseline Clinical Characteristics of ITT[E} Population

Clinical Characteristic	Number of Subjects (%)		
	Study APV29005		Study APV20002
	FPV N=20	FPV/RTV N=89	FPV/RTV N=54
CDC Classification in Children <13 years:	**n=20**	**n=56**	**n=54**
A: Mildly symptomatic	18 (90)	26 (46)	25 (46)
B: Moderately symptomatic	1 (5)	15 (27)	10 (19)
C: Severely symptomatic	0	10 (18)	5 (9)
N: Non symptomatic	1 (5)	5 (9)	14 (26)
CDC Classification in Adults/Adolescents:	**N/A**	**n=31**	**N/A**
A: Asymptomatic		12 (39)	
B: Symptomatic, not AIDS		14 (45)	
C: AIDS		5 (16)	
HIV Risk Factors	**n=20**	**n=89**	**n=54**
Yes	20 (100)	83 (93)	54 (100)
No	0	6 (7)	0
HIV Risk factor Known:	**n=20**	**n=83**	**n=54**
Vertical/Perinatal Transmission	19 (95)	74 (89)	54 (100)
Transfusion	1 (5)	5 (6)	0
Other	0	4 (5)	0
Hepatitis B Test Results:	**n=19**	**n=56**	**N/A**
Non-reactive	19 (100)	51 (91)	
Reactive	0	4 (7)	
Missing	0	0	
Unable to calculate	0	1 (2)	
Hepatitis C Test Results:	**n=19**	**n=56**	**N/A**
Non-reactive	15 (79)	55 (98)	
Reactive	4 (21)	1 (2)	
Missing	0	0	

Adapted from Summary of Clinical Efficacy in Section 3.1.4 Clinical Characteristics

Forty-three percent of subjects in APV20002 had baseline viral loads (plasma HIV-1 RNA copies/mL) of greater than or equal to 500,000 copies/mL (Table 10). Baseline viral load levels were higher in the younger age group. In terms of baseline absolute CD4+ cell counts and percent CD+ cells, the majority had absolute counts greater than or equal to 500 cells/mm^3 and with only 13% of subjects having a percent CD4+ less than 15%.

Table 10: Distribution of Plasma HIV-1 RNA and CD4 Cell Counts at Baseline in the ITT[E] Population in APV20002

	FPV/RTV BID		
	4 weeks to <6 months N=26	6 months to <2 years N=28	Total (N=54)
Baseline HIV-1 RNA			
Median plasma HIV-1 RNA log_{10} c/mL, (IQR)	5.80 (5.17, 6.30)	5.51 (4.81, 5.76)	5.60 (5.00, 6.15)
HIV-1 RNA copies/mL, n (%)			
<400	1 (4)	0	1 (2)
400 to <5000	3 (12)	2 (7)	5 (9)
5000 to <100,000	2 (8)	6 (21)	8 (15)
100,000 to <250,000	1 (4)	4 (14)	5 (9)
250,000 to <500,000	4 (15)	8 (29)	12 (22)
≥500,000	15 (58)	8 (29)	23 (43)
Baseline CD4+ cell counts (absolute)			
Median CD4+ cells/mm^3 (IQR)	1378 (950, 1690)	1120 (874, 1828)	1235 (937, 1795)
CD4+ cells/mm^3, n (%)			
<100	0	0	0
100 to <200	0	0	0
200 to <350	1 (4)	1 (4)	2 (4)
350 to <500	1 (4)	0	1 (2)
≥500	21 (81)	27 (96)	48 (89)
Baseline % CD4+ cells			
Median % CD4+ cells (IQR)	27 (20, 36)	25 (18, 31)	26 (18, 34)
%CD4+ cells, n (%)			
<15	3 (12)	4 (14)	7 (13)
15 to <25	8 (31)	10 (36)	18 (33)
25 to <50	12 (46)	14 (50)	26 (48)
≥50	0	0	0

Source Data: Table 6.14, Table 6.15, and Table 6.16
Baseline value was defined as the value observed at Day 1 visit, or if this is missing, the last value observed before the start of treatment.
IQR=Interquartile Range

Adapted from the APV20002 Study Report in Section 5.4 Demographic and Baseline Characteristics

In APV29005, as seen in Table 11 below, the baseline plasma HIV-1 RNA levels, median CD4+ cell counts and CD4+ percentages were similar among FPV/RTV treated PI-naïve and PI-experienced subjects. The PI-naïve subjects treated with FPV alone had a higher baseline viral load and higher CD4+ count than the other treatment groups. Similar to study APV20002, a significant number of subjects had baseline viral loads

that were greater than or equal to 100,000 copies/mL with 65% of the subjects in the FPV only group and 34% in the FPV/RTV group.

In addition, in APV29005, the proportion of subjects who were treated with FPV/RTV with baseline %CD4+ count less than 15% was 31% (28/89) (27% [13/49] and 38% [15/40] of PI-naïve and PI-experienced subjects respectively); while the corresponding proportion in the FPV group was 11% (2/20). This is also seen in the table below:

Table 11: Distribution of Plasma HIV-1 RNA and CD4 Cell Counts at Baseline by Treatment and PI Status in the ITT[E] Population in APV29005

	FPV	FPV/RTV		
	PI-naïve N=20	PI-naïve N=49	PI-experienced N=40	FPV/RTV Total N=89
Baseline HIV-1 RNA, n	20	49	39	88
Median plasma HIV-1 RNA log_{10} copies/mL, (IQR)	5.1 (4.9, 5.6)	4.7 (4.3, 5.2)	4.5 (4.1, 5.1)	4.7 (4.2, 5.2)
HIV-1 RNA copies/mL, n (%)				
400-<5000	1 (5)	4 (8)	6 (15)	10 (11)
5000-<100,000	6 (30)	29 (59)	20 (51)	49 (56)
100,000-<250,000	7 (35)	9 (18)	10 (26)	19 (22)
250,000-<500,000	2 (10)	2 (4)	3 (8)	5 (6)
≥500,000	4 (20)	5 (10)	0	5 (6)
BaselineCD4+ cell counts (absolute), n	19	49	40	89
Median CD4+ cells/mm^3 (IQR)	810 (460, 1000)	370 (200, 670)	440 (220, 685)	410 (200, 680)
CD4+ cells/mm^3, n (%)				
<100	0	7 (14)	1 (3)	8 (9)
100-<200	0	5 (10)	9 (23)	14 (16)
200-<350	0	11 (22)	4 (10)	15 (17)
350-<500	5 (26)	8 (16)	9 (23)	17 (19)
≥500	14 (74)	18 (37)	17 (43)	35 (39)
Baseline % CD4+ cells, n	19	49	40	89
Median % CD4+ cells (IQR)	19 (18, 27)	21 (14, 29)	24 (11, 30)	21 (12, 29)
% CD4+ cells, n(%)				
<15	2 (11)	13 (27)	15 (38)	28 (31)
15-<25	11 (58)	17 (35)	7 (18)	24 (27)
25-<50	6 (32)	19 (39)	16 (40)	35 (39)
≥50	0	0	2 (5)	2 (2)

Adapted from the APV20005 Study Report in Section 5.4.2 Baseline Characteristics

MO's Comment: Overall, both studies enrolled subjects with baseline clinical characteristics representative of the types of patients that would likely be treated with the study drug.

6.1.3 Subject Disposition

The total number of subjects in these two studies combined was 163 (54 subjects in APV20002, 109 subjects in APV29005). Table 12 below displays the disposition of subjects in the two studies:

Table 12: Disposition on Subjects for APV20002 and APV29005

	Number of Subjects (%)		
	Study APV29005		Study APV20002
	FPV N=20	FPV/RTV N=89	FPV/RTV Total N=54
Ongoing at time of analysis	0	10 (11)	27 (50)
Prematurely discontinued	7 (35)	30 (34)	27 (50)
Reason for discontinuation, n (%)			
Adverse Event	0	4 (4)	2 (4)
Subject decided to withdraw	0	4 (4)	3 (6)
Lost to follow-up	0	0	3 (6)
Protocol violation	0	2 (2)	1 (2)
Insufficient viral load response	5 (25)	5 (6)	3 (6)[a]
Missing	0	1 (1)	0
Other	2 (10)	14 (16)	15 (28)

Data Source: Study APV29005, Table 6.7; Study APV20002, Table 6.4

a. Two of the three subjects with insufficient viral load response were known to have adherence issues (Subjects 8613 and 8659).

Adapted from the Summary of Clinical Efficacy in Section 3.1.1 Subject Disposition

For APV20002, 27 of the total 54 subjects (50%) prematurely discontinued from the study. The most apparent reason for discontinuation was categorized as “other” (15 out of 54 subjects, 28%) however two of the subjects were misclassified; one patient discontinued due to pulmonary tuberculosis and the second was a virological failure. Eight of these subjects discontinued because RTV was unavailable. One subject relocated away from the study site.

In study APV20002, only two subjects discontinued for an AE, one subject had abdominal symptoms and the other developed gastroenteritis and herbal toxicity. These subjects will be discussed in more details in Section 7: Safety Review.

The one protocol violation was a subject who met an exclusion criterion because he had received another investigational drug/therapy within 28 days prior to receiving study medication. This subject was enrolled in the study and received FPV/RTV. Furthermore, this subject received only a single dose of FPV/RTV at the SDV visit. This subject was discontinued because of this protocol violation.

For APV29005, 7 of the 20 subjects (35%) in the FPV only group and 30 of the 89 subjects (34%) in the FPV/RTV treatment group prematurely discontinued from the study. The most common reason for the FPV treatment only group was insufficient viral load response. The most common reason in the FPV/RTV treatment group was "Other". These "other" reasons varied and included poor compliance/adherence, refusal to take the study drug, incarceration, and transition to adult care provider.

In APV29005, there were four subjects who discontinued study medication due to AEs: a 3 year old subject experienced non-serious drug-related Grade 2 vomiting, a 17 year old subject experienced a serious drug-related Grade 2 adverse drug reaction. At the time of this adverse drug reaction, the subject was taking co-trimoxazole and the investigator indicated the adverse reaction had a clinical presentation similar to a co-trimoxazole allergic reaction but could not rule out causality due to FPV or RTV, an 8 year old subject experienced non-serious Grade 3 hypertriglyceridemia, and a 2 year old subject was withdrawn from the study due to an AE confirmed by the site as tuberculosis

The two reported protocol violations were two subjects who had received NNRTIs during the study. Since no start or stop date of these drugs could be verified it was assumed they had received the medications throughout the entire study and were discontinued from the study.

MO's Comment: In both studies there was a significant proportion of subjects that prematurely discontinued. However, the majority of these premature discontinuations were due to reasons that were not related to safety or efficacy and it is unlikely that these discontinuations have affected the overall results of these studies.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint in both studies was proportion of subjects with plasma HIV-1 RNA less than 400 copies/mL and less than 50 copies/mL over time.

The overall outcomes at Week 24 are shown in Table 13 below:

Table 13: Summary of Study Outcomes at Week 24 for ITT[E] Population (MSD=F)

	Study APV29005				Study APV20002
	FPV	FPV/RTV		Total	FPV/RTV
Outcome	PI-naïve N=20 n (%)	PI-naïve N=49 n (%)	PI-experienced N=40 n (%)	N=109 n (%)	Total N=54 n (%)
Virologic success (<400copies/mL plasma HIV-1 RNA)	13 (65)	35 (71)	22 (55)	70 (64)	39 (72)
Primary reason for failure (non-responders)					
Virological failure					
HIV-1 RNA ≥400 copies/mL	3 (15)	5 (10)	6 (15)	14 (13)	7 (13)
Change of background ART	2 (10)	4 (8)	7 (18)	13 (12)	1 (2)
Discontinued study with last HIV-1 ≥400 copies/mL	1 (5)	2 (4)	3 (8)	6 (6)	2 (4)
No virologic data at Week 24 window					
Discontinued study due to an adverse event or death[a]	0	1 (2)	1 (3)	2 (2)	2 (4)
Discontinued study due to other reasons[b]	0	1 (2)	0	1 (<1)	2 (4)
Missing data during window but still on study	1 (5)	1 (2)	1 (3)	3 (3)	1 (2)

Data Source: Study APV29005, Table 7.2; Study APV20002, Table 7.2

a. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

b. In Study APV29005, Subject 192 withdrew consent. In Study APV20002, Subject 7145 discontinued as commercial supply of ritonavir was no longer available and Subject 8605 was lost to follow-up.

Adapted from Summary of Clinical Efficacy in Section 3.2.1 Antiviral Response

For APV20002, 39 of 54 subjects (72%) achieved virologic success as defined as having a viral load less than 400 copies/mL of plasma HIV-1 RNA at Week 24. Ten subjects were deemed virologic failures: seven for having viral loads greater than or equal to 400 copies/mL of plasma HIV-1 RNA at Week 24, one subject because they required a change in their ART background, and two subjects last viral loads were greater than or equal to 400 copies/mL of plasma HIV-1 RNA before they were discontinued from the study.

For APV29005, overall 70 of 109 subjects achieved virologic success which represents 64% of the population in this study. The PI-naïve subjects who received only FPV had a virologic success rate of 65% while in the FPV/RTV treated group, those subjects who were PI-experienced had a lower success rate of 55% as compared to the PI-naïve group (71%). As in the APV20002 study, overall there was a virological failure rate of 13% (14 of 109) because of viral loads greater than or equal to 400 copies/mL. Virological failure represented by change in background ART was significantly higher in APV29005 as compared to APV20002 with a rate of 12%. This may be due to the larger number of PI-experienced subjects in APV29005 which represented the majority of this type of virological failure as compared to the other groups in APV29005. Six percent of virological failures (n=6) had viral loads greater than or equal to 400 copies/mL of plasma HIV-1 RNA before they were discontinued from the study.

MSD=F Analysis of the ITT[E] looking at viral loads less than 50 copies/mL overtime is presented in Table 14 below:

Table 14: Summary of Proportion of ITT[E] Population With Plasma HIV-1 RNA less than 50 copies/mL by Visit

Week	Number of Subjects n/N (%)				
	Study APV29005				Study APV20002
	FPV	FPV/RTV			FPV/RTV
	PI-Naïve N=20 n/N (%)	PI-Naïve N=49 n/N (%)	PI-Experienced N=40 n/N (%)	Total N=89 n/N (%)	Total N=54 n/N (%)
Baseline	0/20	0/49	0/40	0/89	0/54
Week 2	0/20	1/49 (2)	1/40 (3)	2/89 (2)	NA
Week 4	1/20 (5)	4/49 (8)	4/40 (10)	8/89 (9)	1/54 (2)
Week 8	5/20 (25)	7/49 (14)	9/40 (23)	16/89 (18)	NA
Week 12	5/20 (25)	16/49 (33)	12/40 (30)	28/89 (31)	15/54 (28)
Week 16	6/20 (30)	19/49 (39)	11/40 (28)	30/89 (34)	NA
Week 24	8/20 (40)	25/49 (51)	15/40 (38)	40/89 (45)	25/54 (46)

Data Source: Study APV29005, Table 7.12; Study APV20002, Table 7.9

Adapted from Summary of Clinical Efficacy in Section 3.2.1 Antiviral Response

Overall, as expected, the proportions of subjects with viral loads less than 50 copies/mL in both studies was less than the proportions of subjects with viral loads less than 400 copies/mL at Week 24. In APV20002, 25 of 54 subjects (46%) had viral loads less than 50 copies/mL at Week 24. For APV29005, overall 40 of the 89 (45%) subjects had viral loads less than 50 copies/mL with the PI-experienced, FPV/RTV treated group representing the small portion at 38% of the total.

Patients continued to receive study medication and were followed for until Week 48 and beyond. An analysis of patients at Week 48 demonstrated that in study APV20002, the proportion of subjects with viral loads less than 400 copies/mL was 89% (34 of 38 subjects), and 79% (30 of 38 subjects) of those subjects had viral loads less than 50 copies/mL.

Similarly, in APV29005, for the PI-naïve, FPV only group, 14 of 18 subjects (78%) had viral loads less 400 copies/mL and 8 of 18 subjects (44%) had viral loads less than 50 copies/mL at Week 48. In the PI-naïve, FPV/RTV group, 36 of 41 subjects (88%) had viral loads less 400 copies/mL and 31 of 41 subjects (76%) had viral loads less than 50 copies/mL at Week 48. Finally, in the PI-experienced, FPV/RTV group, 22 of 33 subjects (67%) had viral loads less 400 copies/mL at Week 48 and 19 of 33 subjects (58%) had viral loads less than 50 copies/mL at Week 48. Overall, in APV29005, 78% (58 of 74 subjects) achieved viral loads less than 400 copies/mL at Week 48 and 68% (50 of 74 subjects) achieved viral loads less than 50 copies/mL at Week 48.

MO's comment: Overall, the results of both studies show a majority of subjects at all age groups and previous treatment status achieving virologic success as defined as having a viral load less than 400 copies/mL at week 24. In addition, when analyzed at the less than 50 copies/mL mark, in all groups there is was a significant portion of subjects with viral loads less than 50 copies/mL. These results are comparable to those seen in previous studies with adult patients, however most of the adult trials evaluated viral loads of less than 400 copies/mL at 48 weeks.

Changes from baseline in HIV-1 RNA over time

In both studies and in all treatment cohorts, there was a steady and significant decrease from baseline levels in median HIV-1 RNA over time. Across the trials, the baseline median HIV-1 RNA was approximately 5 $\log_{10}$ copies/mL In APV20002, at Week 24, the median change was -3.61 with a range of -3.99 to -2.12. At Week 48, the median change was even greater at -3.73 with a range from -4.26 to -3.00.

For APV29005, overall, the median change from baseline at Week 24 was -2.69, ranging from -3.38 to -1.81. At Week 48, the median change was -2.61 with a range of -3.25 to -1.61. The small change was seen in the PI-experienced group with median changes of -2.28 and -2.14 at Weeks 24 and 48 respectively.

MO's Comment: The consistent and significant change in median viral load from baseline to each study visit over time was consistent with the reductions from baseline observed in previous adult trials.

Changes from baseline in CD4+ cell counts and CD4+ cell percentages over time

As depicted in Table 15 below, in APV20002, the 4 weeks to less then 6 months age group had a median CD4+ cell count increase of approximately 400 cells/mm^3 through Week 24 and 210 cell/mm^3 at Week 48. The median CD4+ cell count increased from 1120 cells/mm^3 at baseline to 1475 cells/mm^3 at Week 24 and 1426 at Week 48 in the 6 months to <2 years age group. The median change from baseline at Week 24 was 278 cells/mm^3 and 251 cells/mm^3 at Week 48.

Table 15: Median CD4+ Cell Count (cell/mm3) and Change from Baseline by Visit and Age Group of APV20002 ITT[E] Population

Week	FPV/RTV BID N=54		
	Median (IQR)	Change from Baseline Median (IQR)	n
4 weeks to <6 months			
Baseline	1378 (950, 1690)	-	23
Week 4	1610 (1170, 2520)	295 (-45, 675)	23
Week 12	1405 (1107, 1757)	200 (-223, 520)	22
Week 24	1595 (1320, 1910)	400 (-270, 750)	22
Week 48	1649 (1150, 2080)	210 (-100, 868)	18
6 months to <2 years			
Baseline	1120 (874, 1828)	-	28
Week 4	1735 (1290, 2287)	331 (-47, 841)	28
Week 12	1822 (1120, 2392)	460 (140, 730)	27
Week 24	1475 (1223, 2178)	278 (-30, 480)	26
Week 48	1426 (1035, 2036)	251 (-255, 587)	20

Adapted from APV20002 Study Report in Section 9.1.3 CD4+ Cell Count

In Table16 below, the change in percent CD4+ cell count from baseline are presented. In the younger age group the median percent CD4+ cell count increased from 27 at baseline to 32% at Week 24 which represented a median percent change of 7%. However at Week 48 there was only a slightly higher increase to 28% with a median percent change of 5%. In the older age group, there was also an increase from baseline of 25% to 32% at Week 24 making a median percent change of 6% and an increase to 34% at Week 48 representing a median percent change from baseline of 6%.

Table 16: Median Percent CD4+ Cell Count Results and Median Percent Change from Baseline by Visit and Age Group in APV20002 ITT[E] Population

Week	FPV/RTV BID N=54		
	Median Percent (IQR)	Median Percent Change from Baseline (IQR)	n
4 weeks to <6 months			
Baseline	27 (20, 36)	-	23
Week 4	29 (23, 37)	3 (-1, 8)	20
Week 12	28 (24, 35)	2 (0, 8)	19
Week 24	32 (27, 34)	7 (-1, 12)	19
Week 48	28 (25, 32)	5 (-7, 9)	15
6 months to <2 years			
Baseline	25 (18, 31)	-	28
Week 4	28 (21, 35)	3 (0, 6)	28
Week 12	32 (23, 39)	6 (2, 8)	27
Week 24	33 (26, 38)	6 (3, 11)	26
Week 48	34 (23, 39)	6 (3, 9)	20

Adapted from APV20002 Study Report in Section 9.1.3 CD4+ Cell Count

For APV29005, similar increases from baseline in median CD4+ cell counts and percent CD4+ cell count. In Table 17, the FPV only group had an increased median change in cell count of 350 cells/mm^3 at Week 24 and 340 cells/mm^3 at Week 48. For the FPV/RTV groups, increased cell counts were seen; for the total number of patients for received both FPV and RTV, a median change of 160 cells/mm^3 was seen at Week 24 and 200 cells/mm^3 at Week 48.

Table 17: Median CD4+ Cells/mm3 Change from Baseline by Visit and PI Status in APV29005 ITT[E] Population

	CD4+ Cell Count Change from Baseline (cells/mm^3) Median [IQR]							
	FPV		FPV/RTV					
Week	PI-naïve N=20	n	PI-naïve N=49	n	PI-exp N=40	n	FPV/RTV Total N=89	n
Week 2	20 [-20, 180]	13	60 [0, 160]	41	90 [2, 190]	32	60 [0, 170]	73
Week 4	130 [-70, 330]	15	90 [23, 150]	43	79 [0, 160]	34	90 [20, 150]	77
Week 8	120 [-120, 250]	19	100 [36, 180]	45	115 [0, 230]	34	110 [10, 227]	79
Week 12	170 [50, 490]	19	180 [60, 261]	45	200 [70, 340]	31	181 [70, 270]	76
Week 16	130 [10, 410]	19	147 [74, 250]	45	135 [0, 250]	34	147 [30, 250]	79
Week 24	350 [110, 640]	18	184 [53, 367]	44	150 [10, 260]	34	160 [40, 324]	78
Week 36	200 [80, 550]	17	232 [68, 396]	42	140 [70, 290]	33	200 [68, 351]	75
Week 48	340 [-30, 470]	17	230 [100, 398]	41	180 [5, 290]	28	200 [50, 350]	69

Adapted from APV29005 Study Report in Section 9.1.3 CD4+ Cell Count Profiles

Predictably, there were also increases in median percent CD4+ cells from baseline at Week 24 and Week 48 for both the FPV only group (7% and 8%, respectively) and the FPV/RTV groups (for total, 6% and 8%, respectively). The smallest changes were seen in the PI-experienced group with only a 5% change at Week 24 and 6% change at Week 48%. This is seen in Table18 below:

Table 18: Median Change from Baseline Percentage CD4+ Cells in APV29005 ITT[E] Population by Visit and PI Status

	% CD4+ Cells Change from Baseline Median [IQR]							
	FPV		FPV/RTV					
Week	PI-naïve N=20	n	PI-naïve N=49	n	PI-exp N=40	n	FPV/RTV Total N=89	n
Week 2	3 [0, 5]	13	1 [-1, 4]	41	2 [0, 5]	32	2 [-1, 4]	73
Week 4	0 [-2, 7]	15	3 [1, 6]	43	3 [1, 4]	34	3 [1, 5]	77
Week 8	4 [-1, 6]	19	4 [2, 6]	45	2 [1, 5]	34	3 [1, 6]	79
Week 12	6 [2, 7]	19	4 [1, 7]	45	3 [2, 7]	31	4 [1, 7]	76
Week 16	4 [0, 8]	19	6 [3, 9]	45	4 [0, 6]	34	4 [2, 8]	79
Week 24	7 [3, 11]	18	8 [4, 10]	44	5 [1, 8]	34	6 [3, 10]	78
Week 36	8 [6, 11]	17	10 [4, 14]	42	6 [3, 8]	33	7 [4, 11]	75
Week 48	8 [4, 11]	17	10 [5, 14]	41	6 [2, 11]	28	8 [4, 12]	69

Adapted from APV29005 Study Report in Section 9.1.3 CD4+ Cell Count Profiles

MO's Comment: Similar to the antiviral responses seen with changes in viral load, the immunologic responses seem to show a significant effect on absolute CD4+ cell counts and percent CD4+ cell counts at both the Week 24 and Week 48 time point.

The decrease in median change from baseline when comparing Week 24 to Week 48 may likely reflect that FPV reaches its maximal effect on antiviral response around Week 24. However, the difference between the two time points may not be significant and the overall change at Week 48 is substantial as compared to baseline.

6.1.5 Analysis of Secondary Endpoints(s)

There were no secondary endpoints in these studies.

6.1.6 Other Endpoints

HIV Disease and Progression and HIV-Associated Conditions

In APV20002, three subjects (6%) experienced HIV disease progression to a new CDC Class C or death. One of these subjects progressed from Class A to Class C (HIV-related encephalopathy). Another subject suffered from septicemia and the last subject had sever gastroenteritis and herbal toxicity and eventually died.

In APV29005, one adolescent/adult (PI-experienced) subject (1.1%) experienced HIV disease progression to CDC Class C or death. This subject experienced progression from one CDC Class C (AIDS) at baseline to a new Class C (cytomegalovirus retinitis)

at Day 434. No HIV disease progression to either a Class C event or death was reported by any children less than 13 years of age.

MO's comment: Since the results of this endpoint are only descriptive it is difficult to interpret their relationship to the efficacy of the study drug.

6.1.7 Subpopulations

Antiviral Response Analyses by Age

As seen in previous sections, similar proportions of subjects in the two age cohorts in APV20002 achieved plasma HIV-1 RNA greater than 400 copies/mL at Week 24, 19of 26 subjects,(73%) in the 4 weeks to 6 months and 20 of 28 subjects (71%) in the 6 months to less than 2 years. A lower proportion of subjects aged 6 months to less than 2 years compared with subjects in the 4 weeks to less than 6 months age group had viral loads of less than 50 copies/mL (11 of 28 subjects, 39% versus 14of 26 subjects, 54%).

In addition, as discussed previously, in APV20002, in the 4 weeks to less months age group there was a greater change in median CD4+ cell count (400 cells/mm^3 versus 278 cells/mm^3). However the median percent CD4+ cell count and median change from baseline were relatively similar.

In APV29005, the 2 to less 6 year old age group in the FPV/RTV treatment group had the largest proportion of subjects (84%, 16 of 19 subjects) with viral loads less than 400 copies/mL at Week 24 compared to the 2 to less than 6 year old age group in the FPV group (65%, 13 of 20 subjects) and the 6 to less than 12 and 12 to 18 year olds in the FPV/RTV group (53%, 16 of 30 subjects and 63%, 25 of 40 subjects, respectively). This is depicted in Table 19 below:

Table 19: Proportion of Subjects with Plasma HIV-1 RNA <400 copies/mL by Visit and Age Group at Entry in APV29005 ITT[E] Population

	FPV	FPV/RTV		
Actual Relative Time	**2 to <6 years N=20 n/N (%)**	**2 to <6 years N=19 n/N (%)**	**6 to <12 years N=30 n/N (%)**	**12 to 18 years N=40 n/N (%)**
Baseline	0/20	0/19	0/30	0/40
Week 2	3/20 (15)	2/19 (11)	5/30 (17)	7/40 (18)
Week 4	5/20 (25)	6/19 (32)	8/30 (27)	17/40 (43)
Week 8	9/20 (45)	10/19 (53)	10/30 (33)	22/40 (55)
Week 12	13/20 (65)	13/19 (68)	14/30 (47)	27/40 (68)
Week 16	12/20 (60)	11/19 (58)	14/30 (47)	22/40 (55)
Week 24	13/20 (65)	16/19 (84)	16/30 (53)	25/40 (63)

Adapted from APV29005 Study Report in Section 9.2.1 Analysis of Antiviral Response by Age Group

For APV29005, the median CD4+ cell count increase from baseline at Week 24 was higher in the 2 to less than 6 year olds in the FPV group (350 cells/mm^3) compared with the 2 to less than 6 year olds (55 cells/mm^3), 6 to less than 12 year olds (235 cells/mm^3) and 12 to 18 year olds (140 cells/mm^3) in the FPV/RTV treatment group.

In addition, median change in percent CD4+ cells from baseline showed increases in all age groups at Week 24. In subjects aged 2 to less than 6 years who receive FPV alone, the percent CD4+ cells increased from 19% at baseline to 31% at Week 24.

For the FPV/RTV treated subjects, the median change ranged from 9% in children aged 2 to less than 6 years to 4% in children aged 6 to less than 12 years. In the 12 to 18 year old age group, the baseline percent CD4+ cell count increased from 15% to 20% by Week 24.

MO's Comment: There does not appear to be a significant difference in age in terms of antiviral and immunologic effects in both studies. Any differences seen may have been impacted by subjects' prior ARV exposure and/or resistance profiles.

Antiviral Response Analyses by Gender

Overall, the proportion of female and male subjects with plasma HIV-1 RNA levels less than 400 copies/mL at Week 24 was similar in both studies as seen in Table 20 below. However there were a limited number of male subjects (n=5) in FPV only treated group in APV29005.

Table 20: Proportion of Subjects with Quantitative Plasma HIV-1 RNA l<400 copies/mL by Visit and Gender for ITT[E] Population

Gender	Number of Subjects n/N (%)					
	Study APV29005				Study APV20002	
	FPV		FPV/RTV		FPV/RTV	
	Female N=15	Male N=5	Female N=43	Male N=46	Female N=31	Male N=23
Baseline	0/15	0/5	0/43	0/46	0/31	1/23 (4)
Week 2	2/15 (13)	1/5 (20)	6/43 (14)	8/46 (17)	NA	NA
Week 4	4/15 (27)	1/5 (20)	15/43 (35)	16/46 (35)	5/31 (16)	6/23 (26)
Week 8	7/15 (47)	2/5 (40)	20/43 (47)	22/46 (48)	NA	NA
Week 12	10/15 (67)	3/5 (60)	27/43 (63)	27/46 (59)	20/31 (65)	11/23 (48)
Week 16	10/15 (67)	2/5 (40)	23/43 (53)	24/46 (52)	NA	NA
Week 24	11/15 (73)	2/5 (40)	27/43 (63)	30/46 (65)	23/31 (74)	16/23 (70)

Adapted from Summary of Clinical Efficacy in Section 3.3.2 Antiviral Response Analyses by Gender

MO's Comment: There does not appear to be a significant difference by gender in terms of antiviral and immunologic effects in both studies; however, it is difficult to draw absolute conclusions because of the limited number of males in the FPV only group in APV29005.

Antiviral Response Analyses by Race

In APV20002, an overwhelming majority of subjects were Black with very small representation all other races. This lack of equal distribution of race precludes any definitive interpretation of the data.

As seen in Table 21 below, In the APV29005 at Week 24, response rates among White/Caucasians receiving FPV/RTV were comparable to the Black population. With all but one subject in the FPV only group being White/Caucasian it is difficult to make any definitive interpretation of racial difference in this study group.

Table 21: Proportion of Subjects with Plasma HIV-1 RNA less than 400 copies/mL by Race at Week 24 for ITT[E] Population

Race	Number of Subjects n/N (%)		
	Study APV29005		Study APV20002
	FPV N=20	FPV/RTV N=89	FPV/RTV N=54
White/Caucasian	12/19 (63)	26/41 (63)	0/2
Black	0	29/43 (67)	32/44 (73)
South Asian	0	1/1 (100)	0
Arabic/North African	0	1/1 (100)	0
Other	1/1 (100)	0/3	7/8 (88)

Adapted from the Summary of Clinical Efficacy in Section 3.3.3 Antiviral Response Analyses by Race

MO's Comment: There does not appear to be a significant difference by race in terms of antiviral and immunologic effects in both studies; however, it is difficult to draw absolute conclusions because of unequal distributions of race.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4) Based on internal discussions between the Clinical Review team and the Clinical Pharmacology team, the Applicant was asked to provide exploration and analysis of dosing recommendations based on weight bands. Weight based dosing could provide more consistent pediatric exposures and more simplified dosing recommendations. This

(b) (4)

Based on simulations based weight, the Applicant found that exposure PK parameters were similar to those based on age. Thus their proposed dosing regimens based on weight (b) (4)

(b) (4)

These (b) (4) regimens provided some exposure data similar to that of adults and antiviral activity was comparable in all age groups. However, while Cmax observed in subjects less than 6 months of age receiving FPV/RTV 45/10 mg/kg BID was comparable to adults, AUC and C_T were 28% and 60% lower respectively. These possible lower exposures could lead to ineffective therapy and viral resistance.

Further analysis looked at scaling the FPV dose for those patients less than 6 months by increasing the dose to 60/7 mg/kg BID for children less than 9 kilograms (kg). While this scaling resulted in an AUC closer to that of adult exposures, there was only a marginal increase in C_T which was still approximately 50% lower as compared to adults. In addition, the Cmax at this dose was almost two times that of adults. From a clinical standpoint, there is a lack of safety data at this higher Cmax. In addition, this dose increase would also result in higher FPV volumes which may be difficult for certain patients to tolerate. For example, children who weighed 8 kg would have to take 9.6 mL of drug at this higher dose as opposed to only 7.2 mL at the proposed dose of 45/7 mg/kg.

After further discussion with the Clinical Pharmacology review team, adjustments to the Applicant's initial dosing recommendations were made. Use of FPV for children less than 6 months and who are PI-experienced was not recommended because of the lack of data since these subjects were not studied. Table 22 lists the final recommended dosage regimens based on weight:

Table 22: Twice-Daily Dosage Regimens for PI-Naïve Pediatric Patients ≥4 Weeks of Age and for PI-Experienced ≥6 Months of Age Using FPV Oral Suspension With Concurrent RTV

Patient's weight	Recommended Dosage Regimen
<11 kg	FPV/RTV 45/7 mg/kg BID[a]
11- <15 kg	FPV/RTV 30/3 mg/kg BID[a]
15- <20 kg	FPV/RTV 23/3 mg/kg BID[a]
≥20 kg	FPV/RTV 18/3 mg/kg BID[a]

[a] When dosing with RTV, do not exceed the adult dose of FPV 700 mg/RTV 100 mg BID

MO's Comment: Please refer the review by Clinical Pharmacology for further details regarding analysis of dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As discussed in previous sections, the antiviral and immunologic responses to Lexiva were shown in a large portion of subjects in both APV20002 and APV29005 at Week 24 and beyond up to Week 48. These results are consistent with previous adult and pediatric studies of Lexiva.

There is no tolerance effect seen with Lexiva or seen in PIs in general. However, for all antiretroviral medications there is the potential for the development of viral resistance with continued but inconsistent exposure.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses.

7 Review of Safety

Safety Summary

Overall, the safety profile seen with FPV in these studies across individual age groups was comparable to the profiles observed in adults. There were no discernable differences seen by treatment group, age or other demographics. Of note, no subjects less than 2 months of age received FPV either alone or in combination with RTV.

The most common AEs were associated with gastrointestinal issues (nausea and vomiting) or infection. SAEs including death were rare and in almost all cases unlikely associated with the use of the study drug.

The laboratory abnormalities were also comparable to those seen in studied adults and previous studied children except for a relative increased incident of neutropenia. In most cases there was a likely confounding factor that contributed to the neutropenia. There were no significant increases seen in other laboratory parameters such as transaminases or lipids that have been seen with the use of FPV or other PIs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As stated previously, two pivotal studies, APV20002 and APV29005, were submitted with evaluation of safety. APV20002 covered subjects 4 weeks to less than 2 years of

age. APV29005 covered subjects 2 to 18 years of age. Study APV20003 was submitted as supportive study and along with APV29005 also provides safety data for subjects 2 to 18 years of age.

7.1.2 Categorization of Adverse Events

The Applicant defined an Adverse Event (AE) by the following:

An AE was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment.

An AE could, therefore, have been any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may have included pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

The Applicant defined a Serious Adverse Event (SAE) by the following:

A serious adverse event was any untoward medical occurrence that, at any dose, resulted in the following outcomes:

- Death
- A life-threatening AE
- Hospitalization or prolongation of existing hospitalization
- Disability/incapacity
- A congenital anomaly/birth defect in the offspring of a treated subject
- Medical events that did not result in death, were not considered life-threatening, or did not require hospitalization, were considered an SAE when, based upon medical or scientific judgment, they could have jeopardized the subject, and required medical or surgical intervention to prevent one of the outcomes listed above
- Abacavir hypersensitive reaction

The Applicant further categorized AEs as Common AEs (AEs with the highest incidence regardless of grade or causality) and Significant AEs (AEs leading to permanent discontinuation of study drug).

Clinical AEs that occurred during the trial were evaluated by the investigator and graded according to either the 1992 modified The Division of AIDS (DAIDS) toxicity grading

scales for Common Adverse Events, or the 2004 grading scales post-protocol amendment.

MO's Comments: The categorization of adverse events and safety coding for this study were appropriate and reported appropriately.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from Studies APV20003 and APV29005 were combined because they provided data in subjects 2-18 years of age. Safety data from Study APV20002 was evaluated separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As seen in Table 23, In APV20002, 54 subjects received FPV/RTV for a median of 574 days with a cumulative exposure of 74 subject-years. The majority of subjects received investigational product for greater than 48 weeks

The integrated safety data of APV29005 and APV20003, 158 subjects received FPV/RTV for a median of 757 days and 20 subjects received FPV for a median of 1461 days. Overall cumulative exposure was 354 subject-years in the FPV/RTV treatment group and 70 subject-years in the FPV treatment group. The majority of subjects received investigational product for greater than 48 weeks.

Table 23: Summary of Exposure to Study Drug for Integrated Safety Analysis of Studies APV29005/APV20003 and APV20002

	APV29005 and APV20003		APV20002
	FPV/RTV (N=158)	FPV (N=20)	FPV/RTV (N=59)
Days on study drug			
n	158	20	54
Median (range)	757 (1–2199)	1461 (106-1759)	574 (8-925)
Weeks on study drug; n (%) subjects			
n	158	20	54
≤2 weeks	3 (2)	0	2 (4)
>2 weeks to 4 weeks	5 (3)	0	0
>4 weeks to 12 weeks	4 (3)	0	3 (6)
>12 weeks to 16 weeks	0	1 (5)	0
>16 weeks to 20 weeks	2 (1)	0	1 (2)
>20 weeks to 24 weeks	1 (<1)	0	1 (2)
>24 weeks to 48 weeks	18 (11)	1 (5)	9 (17)
>48 weeks to 72 weeks	33 (21)	0	7 (13)
>72 weeks to 96 weeks	9 (6)	1 (5)	11 (20)
>96 weeks to 120 weeks	7 (4)	1 (5)	16 (30)
>120 weeks to 144 weeks	9 (6)	0	4 (7)
>144 weeks to 168 weeks	13 (8)	3 (15)	0
>168 weeks to 192 weeks	29 (18)	1 (5)	0
>192 weeks to 216 weeks	10 (6)	3 (15)	0
>216 weeks to 240 weeks	2 (1)	3 (15)	0
>240 weeks	13 (8)	6 (30)	0
Duration of dosing in subject-years[a]	354	70	74

Data Source: ISO, Table 18.1

a. Sum across subjects of treatment stop date minus treatment start date, plus 1, divided by 365.25
Note: The APV20002 FPV/RTV treatment group includes five subjects who only received FPV and/or FPV/RTV at single dose visits

Adapted from the Summary of Clinical Safety in Section 1.2 Overall Extent of Exposure

When exposure is analyzed by age group at entry, the median duration of exposure in subjects less than 2 years of age (574 days) and 12 to 18 years of age (659 days) was lower than in subjects 2 to less than 6 years of age (1043 days) and 6 to less than 12 years of age (841 days) seen in Table 24.

Overall cumulative exposure was highest in the 12 to 18 years age group and lowest in the less than 2 years age group from APV20002. Across all age groups the majority of subjects had received investigational product(s) for >48 weeks.

Table 24: Summary of Exposure to Study Drug by Age Group at Entry for Integrated Safety Analysis of APV29005/APV20003, and for APV20002

	APV29005 and APV20003			APV20002
	2 to <6 years (N=56)	**6 to <12 years (N=47)**	**12 to 18 years (N=75)**	**<2 years (N=59)**
Days on study drug				
n	56	47	75	54
Median (range)	1043 (15–2199)	841 (1–1868)	659 (2–1881)	574 (8–925)
Weeks on study drug; n (%) subjects				
n	56	47	75	54
≤2 weeks	0	2 (4)	1 (1)	2 (4)
>2 weeks to 4 weeks	2 (4)	2 (4)	1 (1)	0
>4 weeks to 12 weeks	0	3 (6)	1 (1)	3 (6)
>12 weeks to 16 weeks	1 (2)	0	0	0
>16 weeks to 20 weeks	0	0	2 (3)	1 (2)
>20 weeks to 24 weeks	0	0	1 (1)	1 (2)
>24 weeks to 48 weeks	6 (11)	5 (11)	8 (11)	9 (17)
>48 weeks to 72 weeks	8 (14)	5 (11)	20 (27)	7 (13)
>72 weeks to 96 weeks	3 (5)	3 (6)	4 (5)	11 (20)
>96 weeks to 120 weeks	4 (7)	3 (6)	1 (1)	16 (30)
>120 weeks to 144 weeks	1 (2)	5 (11)	3 (4)	4 (7)
>144 weeks to 168 weeks	5 (9)	3 (6)	8 (11)	0
>168 weeks to 192 weeks	4 (7)	10 (21)	16 (21)	0
>192 weeks to 216 weeks	6 (11)	2 (4)	5 (7)	0
>216 weeks to 240 weeks	5 (9)	0	0	0
>240 weeks	11 (20)	4 (9)	4 (5)	0
Duration of dosing in subject-years[a]	155	105	164	74

Data Source: ISO, Table 18.3

a. Sum across subjects of treatment stop date minus treatment start date, plus 1, divided by 365.25

Note: The APV20002 FPV/RTV treatment group includes five subjects who only received FPV and/or FPV/RTV at single dose visits

Adapted from the Summary of Clinical Safety in Section 1.2.1 Exposure by Age Group at Entry

Demographics and clinical characteristics, for APV20002 and APV29005, were discussed in full detail in Section 6.1.2 above. For APV20003, 69 subjects were analyzed. The mean age was 10.2 years with a range of 2 to 17 years. There was a slight female predominance with 39 females (57%) and 30 males (43%) The majority of subjects were either White/Caucasian (51%) or Black (35%).

MO's Comment: The exposure data appears appropriate for all treatment and studied age groups. Lower exposures in certain cohorts were likely due to limited numbers of subjects enrolled in those cohorts. In addition, as previously discussed there no subjects studied less than 2 months of age. Any safety conclusions made are speculative based on extrapolation of older pediatric patients and previous experience with other PI such as lopinavir-ritonavir.

7.2.2 Explorations for Dose Response

No further data was submitted to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing included in this study.

7.2.4 Routine Clinical Testing

For all three studies submitted, safety was assessed by both laboratory and clinical evaluations. Clinical AEs and laboratory AEs were graded according to the modified DAIDS toxicity grading guidelines.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new in vitro or in vivo assessment data was submitted regarding metabolic, clearance, or interaction work up.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most common AEs seen with the protease inhibitor drug class include gastrointestinal intolerance, lipodystrophy and lipid abnormalities. The routinely scheduled assessments by both laboratory and clinical data at clinic visit were appropriate to assess the most common side AEs seen with PIs.

7.3 Major Safety Results

Safety results were primarily based on data integrated safety analysis of APV20002, APV29005 and APV20003.

7.3.1 Deaths

A total of three deaths were reported, all in APV20002. The following are narrative descriptions of these cases:

A 24 month old male died (b) (6) days after a single dose of FPV and (b) (6) days after a single dose of FPV/RTV. The investigator reported that the subject died due to an acute abdominal disorder with acute abdominal pain and vomiting of unknown etiology as secondary events. The investigator did not consider the event to be related to the investigational products.

A 19 month old female on Day (b) (6) experienced Grade 4 septicemia and died despite resuscitation. The investigator did not consider the event to be related to the investigational products. The last dose of the study drug was taken the day before the event occurred.

A 2 month old male had Grade 4 gastroenteritis and poisoning from a traditional herbal medicine. The AE was reported as starting on Day (b) (6). The traditional herbal medicine was administered 3 days before the events while FPV, RTV and abacavir were initiated 7 days before the events. The subject had presented the day before the death, with a history of diarrhea and was asked to return the next day. Hospital records indicated a history of diarrhea, vomiting, cough and shortness of breath. The subject died on the day of admission. The investigator considered that there was a reasonable possibility that the acute gastroenteritis may have been caused by FPV and RTV and that there was no reasonable possibility that the traditional herbal medicine poisoning may have been caused by FPV and RTV. The death certificate cited 'death from natural causes'.

MO's Comment: After review of the details of these three cases, I agree with the assessment of the investigators in each case that it was unlikely that the study drug contributed to the death of these subjects.

Nonfatal Serious Adverse Events

In Table 25 below, some of the most common SAEs in all three studies:

Table 25: Summary of the Most Common Nonfatal SAEs for Integrated Safety Analysis of Studies APV29005/APV20003 and for APV20002

	Number (%) of Subjects		
	APV29005 and APV20003		APV20002
SAE	**FPV/RTV (N=158)**	**FPV (N=20)**	**FPV/RTV (N=59)**
Any event	31 (20)	5 (25)	20 (34)
Drug hypersensitivity	9 (6)	3 (15)	0

Pyrexia	3 (2)	0	0
Pneumonia	3 (2)	1 (5)	5 (8)
Gastroenteritis	1 (<1)	1 (5)	5 (8)
Respiratory tract infection	1 (<1)	1 (5)	0
Bronchopneumonia	0	0	4 (7)
Measles	3 (2)	0	0
Urinary tract infection	1 (<1)	0	2 (3)
Hypertension	0	0	2 (3)
Abdominal symptom	0	0	1 (2)

Adapted from the Summary of Clinical Safety in Section 2.1.3 Other Serious Adverse Events

In APV20002, SAEs were reported for 34% (20 of 59 subjects), with pneumonia, gastroenteritis and bronchopneumonia the most frequently reported (8%, 8% and 7% of subjects, respectively).

In the integrated data from APV29005 and APV20003, SAEs were reported for 20% (31 of 158 subjects in the FPV/RTV group. In the FPV treatment group, SAEs were reported for 25% (5 of 20 subjects). The most frequent SAE was drug hypersensitivity, reported in 6% of subjects who received FPV/RTV and in 15% of subjects who received FPV. All serious cases of drug hypersensitivity were attributed to abacavir.

Not depicted in Table 25 above, the majority of SAEs were each reported in one subject only.

MO's Comment: The SAEs seen in these studies were rare and likely not associated with the study drug. They are also consistent with SAEs seen in previous studies with Lexiva. There are no major concerns in terms of SAEs.

7.3.3 Dropouts and/or Discontinuations

In APV20002, no subjects discontinued due to AEs. . Two subjects experienced fatal AEs and these cases were reported as discontinuation due to an AE on the investigational product discontinuation Case Report Form (CRF) page. However, the AE CRF page was completed with 'Not Applicable' as the action taken with study drug, rather than 'Withdrawn'. A third subject only participated in an SDV but completed the investigational product discontinuation CRF page to say that investigational product was discontinued due to AE. However, on the AE page 'Not Applicable' was reported for 'action taken'.

For APV29005 and APV20003, 16 (1%) subjects reported AEs that led to premature discontinuation. All of these subjects were in the FPV/RTV group. The most common AEs were for gastrointestinal (nausea and vomiting) reasons.

7.3.4 Significant Adverse Events

As described in Section 7.3.3 and depicted in Table 26 below, significant AEs that lead to discontinuation of study drug were only seen in those patients who received boosted FPV in integrated data group. Review of the individual studies (APV29005 and APV20003) showed that fewer subjects discontinued prematurely due to AEs in APV29005 (4%, 4 of 109 subjects) as compared to APV20003 (17%, 12 of 69 subjects).

Table 26: Summary of AEs Leading to Permanent Discontinuation of Study Drug for APV29005/APV20003 and for APV20002

	Number (%) of Subjects		
Adverse Event Leading to Permanent Discontinuation of Study Drug	**APV29005 and APV20003**		**APV20002**
	FPV/RTV (N=158)	**FPV (N=20)**	**FPV/RTV (N=59)**
Any event	16 (10)	0	0
Vomiting	4 (3)	0	0
Nausea	3 (2)	0	0
Hypertriglyceridemia	2 (1)	0	0
Abdominal discomfort	1 (<1)	0	0
Hyperglycemia	1 (<1)	0	0
Blood alkaline phosphatase increased	1 (<1)	0	0
Eosinophil count increased	1 (<1)	0	0
Adverse drug reaction	1 (<1)	0	0
Pyelonephritis	1 (<1)	0	0
Hodgkin's disease	1 (<1)	0	0
Hemoptysis	1 (<1)	0	0

Adapted from the Summary of Clinical Safety in Section 2.1.4.1 Adverse Events Leading to Discontinuation of Study Drug

MO's Comment: The increased incidence of significant AEs in APV20003 may be due to the fact that the duration of this study was longer and median exposure to study drugs was also longer. The some of the increased episodes of vomiting and nausea seen in the the FPV/RTV group as compared to the FPV group in APV29005/APV20003 may have been due to the addition of RTV.

7.3.5 Submission Specific Primary Safety Concerns

Overall, there are no specific safety concerns for this study drug. The significant SAEs and deaths seen in these studies are unlikely due to study drug and were rare. The overall safety profile is consistent with previous adult studies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In APV20002, the highest incidences of AEs by organ system were infections and infestations (88%, 52 of 59 subjects) and gastrointestinal disorders (59%, 35 of 59 subjects) as seen in Table*. The most commonly reported individual AEs were diarrhea (47%, 28 of 59 subjects), upper respiratory tract infection (34%, 20 of 59 subjects), gastroenteritis (31%, 18 of 59 subjects), nasopharyngitis and pharyngitis (both 27%, 16 of 59 subjects), rhinitis (25%, 15 of subjects 59), otitis media (22%, 13 of 59 subjects) and vomiting (20%, 12 of 59 subjects).

Specifically for the FPV/RTV treated patients, for the integrated data from APV29005 and APV20003, the highest incidences of AEs by organ system were infections and infestations (72%, 114 of 158 subjects) and gastrointestinal disorders (66%, 105 of 158 subjects). The most commonly reported individual AEs were vomiting (35%, 56 of 158 subjects), cough (31%, 49 of 158 subjects), diarrhea (28%, 44 of 158 subjects), upper respiratory tract infection (23%, 36 of 158 subjects), pyrexia (20%, 32 of 158 subjects), and headache (20%, 32of 158 subjects).

Specifically for the FPV only treated patients, for the integrated data from APV29005 and APV20003, the highest incidences of AEs by organ system were also infections and infestations (75%, 15 of 20 subjects) and gastrointestinal disorders (65%, 13 of 20 subjects). The most commonly reported individual AEs were respiratory tract infections (65%, 13 of 20 subjects) and vomiting (60%, 12 of 20 subjects).

Table 27: Summary of Adverse Events by System Organ Class (in at least 10% of Subjects in any Treatment Group) of APV29005/APV20003, and for APV20002

	Number (%) of Subjects		
	APV29005 and APV20003		APV20002
Adverse Event	**FPV/RTV (N=158)**	**FPV (N=20)**	**FPV/RTV (N=59)**
Any Event	149 (94)	19 (95)	54 (92)
Infections and Infestations	114 (72)	15 (75)	52 (88)
Upper respiratory tract infection	36 (23)	3 (15)	20 (34)
Nasopharyngitis	27 (17)	1 (5)	16 (27)
Bronchitis	24 (15)	3 (15)	7 (12)
Rhinitis	16 (10)	2 (10)	15 (25)
Otitis media	18 (11)	0	13 (22)
Gastroenteritis	10 (6)	1 (5)	18 (31)
Pharyngitis	12 (8)	1 (5)	16 (27)
Respiratory tract infection	4 (3)	13 (65)	1 (2)
Ear infection	13 (8)	3 (15)	0
Tonsillitis	7 (4)	1 (5)	7 (12)
Pneumonia	6 (4)	3 (15)	5 (8)
Otitis media acute	4 (3)	1 (5)	7 (12)
Bronchiolitis	0	0	6 (10)
Gastrointestinal	105 (66)	13 (65)	35 (59)
Vomiting	56 (35)	12 (60)	12 (20)
Diarrhea	44 (28)	2 (10)	28 (47)
Nausea	26 (16)	1 (5)	1 (2)
Respiratory, Thoracic and Mediastinal	74 (47)	1 (5)	14 (24)
Cough	49 (31)	1 (5)	10 (17)
Skin and Subcutaneous Tissue	56 (35)	5 (25)	21 (36)
Rash[a]	23 (15)	0	4 (7)
Eczema	5 (3)	1 (5)	6 (10)
Dermatitis diaper	1 (<1)	0	7 (12)
Dermatitis allergic	1 (<1)	4 (20)	1 (2)
General Disorders and Administration Site Conditions	45 (28)	1 (5)	4 (7)
Pyrexia	32 (20)	1 (5)	4 (7)
Investigations	27 (17)	3 (15)	14 (24)
Aspartate aminotransferase increased[b]	3 (2)	2 (10)	0
Alanine aminotransferase increased[b]	1 (<1)	2 (10)	1 (2)

Data Source: ISO, Table 18.9
Continued
a. 'Rash' preferred term only.
b. Increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) both include a report of ALT decreased and AST decreased that were confirmed as increases by the investigator.
c. All cases except two were attributed to abacavir.

Adapted from the Summary of Clinical Safety in Section 2.1.1 Common Adverse Events

(Continued) Table 27 Summary of Adverse Events by System Organ Class (in at least 10% of Subjects in any Treatment Group) of APV29005/APV20003, and for APV20002

Nervous System	36 (23)	0	2 (3)
Headache	32 (20)	0	0
Eye	22 (14)	0	12 (20)
Conjunctivitis	12 (8)	0	10 (17)
Blood and Lymphatic System	20 (13)	5 (25)	7 (12)
Anemia	4 (3)	2 (10)	0
Immune System	14 (9)	5 (25)	0
Drug hypersensitivity[c]	10 (6)	4 (20)	0

Data Source: ISO, Table 18.9

a. 'Rash' preferred term only.
b. Increased alanine aminotransferase and increased aspartate aminotransferase both include a report of ALT decreased and AST decreased that were confirmed as increases by the investigator.
c. All cases except two were attributed to abacavir.

Adapted from the Summary of Clinical Safety in Section 2.1.1 Common Adverse Events

MO's Comment: Many of the common AEs seen in these studies are likely not associated with the study drug. They are consistent with common AEs seen in previous studies with Lexiva. There are no major concerns in terms of common AEs.

7.4.2 Laboratory Findings

Table 28 below, summarizes all treatment-emergent Grade 3/4 laboratory toxicities for this safety analysis.

In APV20002, only two Grade toxicities (4%, 2 out of 51 subjects) were reported for abnormalities in alanine aminotransferease (ALT). No Grade 3/4 toxicities were reported in aspartate aminotransfersase (AST). In addition, there were 5 reports of neutropenia representing 10% of subjects with evaluable data. No other significant Grade 3/4 lab abnormalities were seen.

Analysis of the integrated data of APV29005 and APV20003, showed in all parameters of special interest that 12% (18 of 158 subjects) of the FPV/RTV group reported Grade 3/4 toxicities and 10% (2 of 20 subjects) of the FPV only reported Grade 3/4 toxicities. Toxicity in low density lipoprotein cholesterol was the most frequent overall and within the FPV/RTV group. In the FPV only group, the most frequent toxicity was in ALT and AST with 2 of 10 subjects (10%) reporting Grade 3/4 toxicities for both laboratory parameters.

In addition, neutropenia was reported in 13% (20 of 150 subjects) in the FPV/RTV group and 40% (8 of 20 subjects) in the FPV only group.

Table 28: Summary of Treatment-Emergent Grade 3/4 Laboratory Toxicities for APV29005/APV20003 and APV20002

	APV29005 and APV20003		APV20002
	FPV/RTV (N=158) n/N (%)	FPV (N=20) n/N (%)	FPV/RTV (N=59) n/N (%)
Laboratory Parameter	Grade 3/4	Grade 3/4	Grade 3/4
All Parameters of Special Interest	18/153 (12)	2/20 (10)	2/51 (4)
Alanine aminotransferase (U/L)	4/153 (3)	2/20 (10)	2/51 (4)
Aspartate aminotransferase (U/L)	5/153 (3)	2/20 (10)	0/51
Total bilirubin (Umol/L)	0/153	0/20	0/51
Total cholesterol (mmol/L)	3/150 (2)	0/19	0/49
Glucose elevated (mmol/L)	0/153	0/20	0/51
LDL cholesterol (mmol/L)	8/150 (5)	0/19	0/49
HDL cholesterol (mmol/L)	0/150	0/19	0/49
Lipase (U/L)	0/149	0/19	0/10
Triglycerides (mmol/L)	1/150 (<1)	0/19	0/49
All Parameters Other Than Special Interest: Clinical Chemistry	13/153 (8)	4/20 (20)	7/51 (14)
All Parameters Other Than Special Interest: Hematology	23/151 (15)	8/20 (40)	6/51 (12)
Neutrophils (GI/L)	20/150 (13)	8/20 (40)	5/51 (10)

Data Source: m2.7.4, Table 30
n/N: number of subjects with event/number of subjects with evaluable data
LDL: low density lipoprotein; HDL: High density lipoprotein.

Adapted from the Summary of Clinical Safety in Section 3.1 Treatment-Emergent Grade 3/4 Laboratory Abnormalities

When analyzed by age there were no major differences seen.

As the Applicant alludes to, there was a higher incidence of neutropenia in these pediatric studies than seen in previous adult studies (3% in adults). Narratives of theses abnormalities were provided and reviewed.

For APV20002, the cases of neutropenia occurred at variable times during the study and with varying confounding factors including concurrent use of zidovudine and acute presumed infection. Only one case required a dose reduction, and the others resolved with continued treatment with FPV. Based on the pattern of the abnormalities the Applicant suggested that the neutropenia was related to FPV.

For APV29005, the cases of neutropenia occurred developed later in the study. Thirteen of the 15 cases were while subjects were on concomitant ARVs that may have

contributed to the neutropenia. Based on the pattern of the abnormalities the Applicant suggested that the neutropenia was related to FPV.

For APV20003, there were no clear factors that may have contributed to the neutropenia except for subjects who were on concomitant medications that can cause neutropenia. The Applicant was unsure of the association with FPV.

MO's Comment: Overall, the laboratory abnormalities seen in these studies were comparable to those seen in previous adult studies. More common abnormalities seen with previous studies of FPV and other PIs such as elevated transaminases or lipid abnormalities were not seen with increased frequency.

The relative increased frequency of neutropenia in these pediatric patients as compared to that in adults and previous studied children is somewhat explained with the smaller number of subjects and confounding factors. However this pattern of neutropenia suggests a possible relationship with treatment with FPV and may be a parameter that needs further post-marketing monitoring.

7.4.3 Vital Signs

The vital signs that were assessed include height, weight, and systolic and diastolic blood pressure.

For height and weight, increases in median height and weight were observed in all studies and were appropriate and as expected for these subjects.

In terms of blood pressure, minimal median changes to both systolic and diastolic blood pressures over time were observed in all studies.

MO's Comment: There are no concerns for study drug effects on vital signs.

7.4.4 Electrocardiograms (ECGs)

No data regarding ECGs was submitted. Lexiva is not known to cause QTc prolongation.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials submitted.

7.4.6 Immunogenicity

There are no specific immunogenicity issues.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no dose dependency as adverse events occurred with similar frequency and severity across all disease and age groups.

7.5.2 Time Dependency for Adverse Events

There was no time dependency as adverse events occurred with similar frequency and severity across all disease and age groups.

7.5.3 Drug-Demographic Interactions

There were no specific drug-demographic interaction studies or analyses. However, in the integrated safety analysis of APV29005 and APV20003, evaluation of AEs by race showed that vomiting was more frequent in White/Caucasian subjects (49%, 47 of 95 subjects) than in Black subjects (22%, 15 of 67 subjects). Nineteen subjects in the FPV treatment group were White and a high incidence of vomiting was seen in this treatment group which may partially explain the higher incidence of vomiting in White subjects.

7.5.4 Drug-Disease Interactions

No new information or data was submitted regarding drug-disease interactions.

7.5.5 Drug-Drug Interactions

Drug-drug interaction data for Lexiva is included in the currently approved labeling. No new information or data was submitted regarding drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information or data was submitted regarding carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

No new information or data was submitted regarding human reproduction or pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety assessment of pediatrics is as stated above. In APV20002 and APV29005/APV20003 changes and height and weight were monitored. As expected, increases in median height and weight were observed in both studies. No major safety issues were seen on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There has been no new information or data submitted to assess the abuse, overdosing or withdrawal and rebound potential of FPV.

7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues.

8 Postmarket Experience

According to the Applicant, worldwide marketed exposure from first launch in 2003 to March 2011 is estimated to be 295,256 subject-years using (b) (4) sales volumes data and assuming a standard daily dose of 1400 mg. The oral suspension represented less than 1% of total FPV sales.

Cumulative data collected until May 31, 2011 showed 15 spontaneous reports (approximately 3% of all FPV spontaneous reports) were identified on the marketing authorization holder (MAH) global adverse event database where FPV was reported as a suspect drug in subjects less than 18 years of age. However, 8 of these 15 cases described in utero exposure to FPV rather than direct administration of FPV.

Of the remaining seven cases, four cases were assessed as “serious” based on FDA criteria. Ages ranged from 7 to 17 years with no cases reported of younger children. Doses ranged from 1000 mg to 2100 mg and four cases received concurrent RTV.

AEs included gastrointestinal events, rash, lactic acidosis, tubulonephritis, and Cushing-like syndrome. Some of these cases had confounding factor that may have contributed to the development of these AEs.

Currently, the Applicant is conducting an observational cohort study in HIV-infected children and adolescents using data from the European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) cohorts. This study seeks to assess the safety of European Union (EU) licensed doses of FPV/RTV in real world population. This mainly covers patients aged 6 to 18 years of age. To date, this study has not detected any signals which would raise safety concerns.

MO's Comments: Pediatric post-marketing safety data thus far has not detected any concerning safety signals. In addition, there has been no new safety signal identified in adults that is concerning for pediatric patients. Collection and evaluation of post-marketing safety data should continue especially for those younger children (less than 6 months of age) of which there is a paucity of safety data. Neutropenia should be added to routine monitoring in pediatric patients.

9 Appendices

9.1 Literature Review/References

1. AIDSinfo Guidelines for the Use of Antiretroviral Agents in Pediatric HIV infection
http://www.aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0/

2. Lexiva® label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021548s029,022116s013lbl.pdf

9.2 Labeling Recommendations

Please see final label draft for full detail.

The following labeling recommendations to the following sections have been made:

Indications and Usage

- The statement, “Twice-daily dosing of LEXIVA plus ritonavir is not recommended for protease inhibitor experienced pediatric patients less than 6 months of age” was added.

Dosage and Administration

- In sub-section 2.2 Pediatric Patients (Aged 4 Weeks to 18 Years), the above statement was also added
- A table with the recommended twice-daily dosage regimens for PI-naïve pediatric patients older than 4 weeks of age and for PI-experienced pediatric patients older 6 months of age using Lexiva Oral Suspension with concurrent ritonavir was added.

Adverse Reactions

- Safety data from the three pediatric studies was added including the increased incidence of vomiting and neutropenia as compared to the incidence seen in adult subjects.

Use In Specific Populations

- A statement that the safety, PK profile, virologic and immunologic responses of Lexiva with and without ritonavir were studied in pediatric subjects aged at least 4 weeks to less than 18 years of age and weighing at least 3 kg.
- In addition, a statement that the adverse reaction profile seen in these subjects was similar to adults was added.

- A statement regarding that treatment with Lexiva is not recommended in PI-experienced patients less than 6 months of age.
- A statement that the PK, safety, tolerability and efficacy of Lexiva in patients less than 4 weeks of age have not been established was added.
- A statement that sufficient data is not available to recommend once-daily dosing of Lexiva alone or in combination with RTV for any pediatric patients was added.

Clinical Pharmacology

- In sub-section 12.3 Pharmacokinetics in the Pediatric Patients section, data regarding the pediatric PK studies results was added including the rationale for why Lexiva is not recommended for PI-experienced patients aged less than 6 months.
- The Applicant was asked to supply a table that summarizes APV exposures achieved in pediatric subjects based on weight band dosing recommendations.

Clinical Studies

- In sub-section 14.3 Pediatric Patients, efficacy data including viral load and CD4+ cells counts from the two pivotal studies was added.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this submission.

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/s/

NEIL G RELLOSA
04/04/2012

RUSSELL D FLEISCHER
04/04/2012